IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

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| Schiemann et al. | | Group Art Unit: | 1625 |
| Serial No.: | 10/583,689 | Examiner: | Rita J. Desai |
| Filed: | Dec. 14, 2004 | | |
| For: | 2-(Hetero)-aryl substituted tetrahydrochinoline | | |

**DECLARATION UNDER 37 C.F.R. § 1.132**

Honorable Commissionar of
Patents and Trademarks
Washington, D.C. 20231

SIR:

Kai Schiemann, being duly warned, deposes and says:

I am a citizen of Germany residing at Seeheim-Jugenheim, Germany;

I am a chemist by training and experience;

the degree of Dr. rer. nat. was bestowed on me by the University of Göttingen, Germany in 1995;

from 1993 to 1995 I was employee at the Institute of organic chemistry at the University of Göttingen, Germany;

from 1995 to 1996 I was postdoctoral fellow at the Department of Chemistry, University of California, Santa Cruz, CA, USA;

from 1997 to 1999 I was postdoctoral fellow at Parke Davis, Warner-Lambert, Ann Arbor, MI, USA;

since February 1999 I am Head of a chemical laboratory of Merck Serono, Merck KGaA, Darmstadt, Germany;

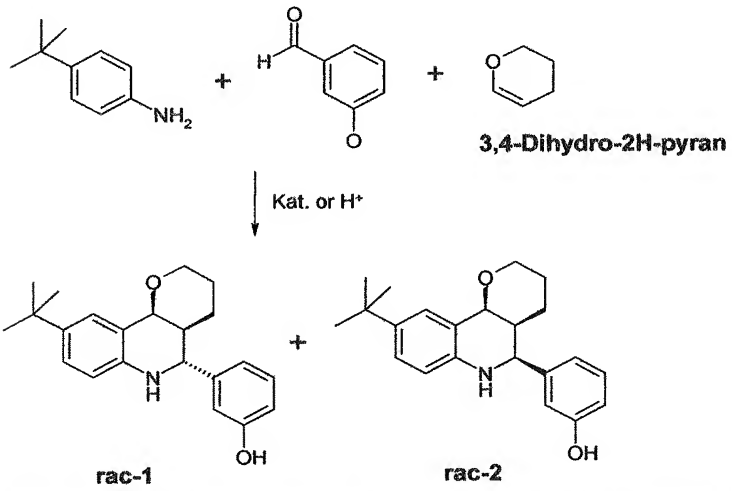
I am author or co-author of numerous papers and patents in the fields of medicinal and/or organic chemistry.

The synthesis routes presented below for the present application prove that the claimed compounds could be synthesized according to the disclosure and knowledge at the date of filing this application. The starting materials were known in the literature and commercially available and the compounds of the invention were prepared via known routes under formation of known intermediates.

I have carried out, or supervised experiments for preparing the claimed compounds according to the methods described within the genus claimed in the pending application.

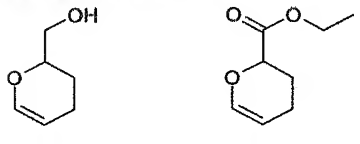
## Report on synthesis

In close analogy to the reaction described in WO2005063735 (see scheme 1), substituted 3,4-dihydro-2H-pyrans were used instead of the plane 3,4-dihydro-2H-pyran. Exactly the same reaction conditions described can be used.



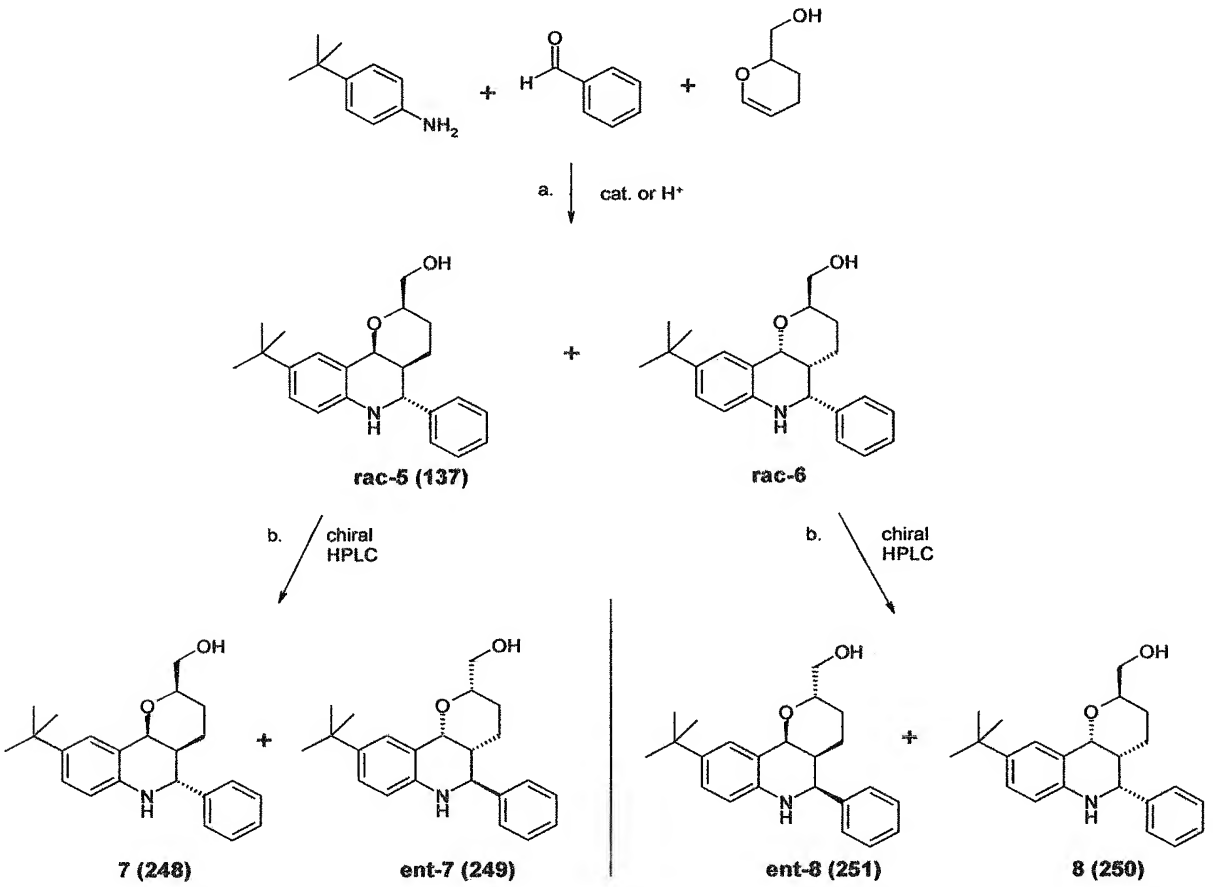

Scheme 1: Synthetic scheme published in WO2005063735

More precisely commercially available (3,4-dihydro-2H-pyran-2-yl)-methanol **3** and 3,4-dihydro-2H-pyran-2-carboxylic acid ethyl ester **4** were used according to the procedure described in WO2005063735.




**3** **4**

In the reaction with **3** (see Scheme 2) 2 major diastereomeres were formed, which could be separated by chromatography. The resulting pure diastereomeres were then separated by chiral HPLC.

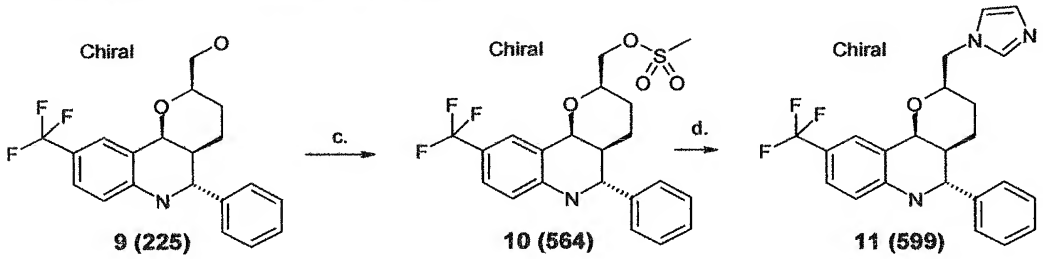



**a.** A solution of the mono trifluoroacetic acid salt of 4-*tert*-butylamine in acetonitrile -previously prepared by dissolving 4-tert-butylamine (12.0 g, 79.6 mmol) in acetonitrile (90 mL) and adding slowly trifluoroacetic acid (6.13 mL; 79.6 mmol) at 0°C – was added to a solution of benzaldehyde (8.45 g, 79.6 mmol) and (3,4-dihydro-2H-pyran-2-yl)-methanol (9.09 g, 79.6 mmol) in acetonitrile (50 mL) at 0°C. The solution was stirred for 60 min at 0°C and warmed to room temperature. The solvent was removed in vacuo. The residue was directly purified by chromatography (petrol ether/dichloromethane, 3:2). 9.20 g (26.2 mmol, 33 %) of a colorless solid identified as compound **rac-5** and 7.62 g (21.7 mmol, 27 %) of **rac-6** also as a colorless solid were obtained.
According to this reaction the following racemic and/or diastereomeric mixtures were prepared: 60, 120, 121, 122, 126, 127, 137, 138, 167, 193, 199, 200, 209, 237, 238, 252, 271, 292, 293, 315, 323, 324, 329, 335, 342 and 350.

b. 200 mg **rac-5** was dissolved in 10 mL of hot ethanol/heptane (1:1) and injected into the HPLC injector as hot solution. The compound was eluated with ethanol/heptane (1:9) using 2

consecutive columns (Hibar 25x5cm Chiralpak AD 20µm). After evaporation of the solvent 87 mg of **7** and 85 mg of **ent-7** were obtained both as colorless solids.
This process was repeated several times to isolate greater amounts of material used in the following reactions.
According to this separation method the following enantiomerically enriched or pure compounds were prepared: 225, 226, 248, 249, 250, 251, 265, 266, 267, 268, 275, 276, 278, 283, 319, 320, 327, 328, 340, 341, 351, 357, 358, 363, 364, 365, 366, 596, 597, 641, 646 and 647.

The alcohol was derivatized according to the well-known literature and known to the experienced chemist. The primary alcohol was activated with methane sulfonyl chloride and exchanged with nucleophiles, e.g.

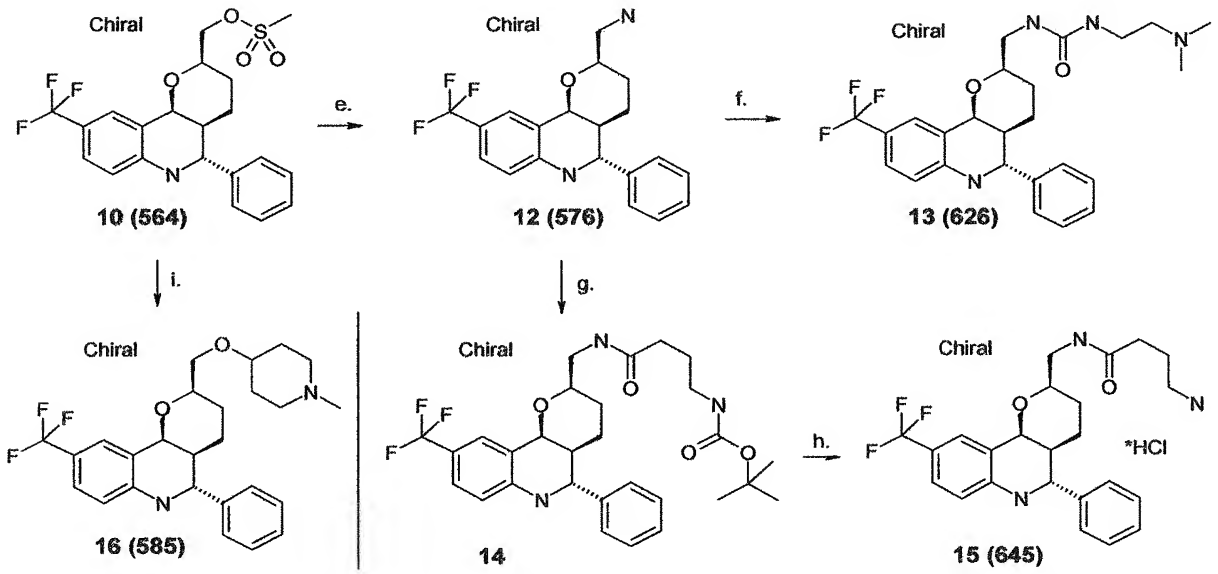



**9 (225)** **10 (564)** **11 (599)**

c. The alcohol **9** (1.00 g, 2.75 mmol) was suspended in dichloromethane (DCM, 20 mL), triethyl amine (0.76 mL, 5.50 mmol) was added at RT, followed dropwise by methane sulfonyl chloride (0.23 mL, 3.03 mmol) dissolved in DCM (5 mL) at RT. The solution was stirred overnight at the same temperature and the solvent was evaporated in vacuo. The residue was redissolved in ethyl acetate (100 mL) and extracted with water twice. The organic phase was dried with sodium sulfate, filtered and evaporated to dryness. 1.20 g (2.72 mmol, 99%) of a colorless solid identified as **10** were obtained. The crude product was used in the next reaction without further purification.
According to this procedure compound 648 was synthesized. Since these methanesulfonic esters are reactive intermediates the other derivatives were not characterized in detail.

d. Compound **10** (100 mg, 0.23 mmol) was dissolved in 1-methyl pyrollidinone (2 mL), imidazole (50.0 mg, 0.73 mmol) was added at RT and the mixture was stirred at 100°C in a sealed pressure tube for 18 h. The reaction mixture was poured on water and the crystals formed were collected and dried. The crystals were dissolved in 0.1 M HCl in isopropanol (0.1 mL), the solvent was evaporated in vacuo and the residue crystallized from diethyl ether. 82 mg (0.20 mmol, 86%) of **11** as a colorless solid were obtained.
According to this procedure the following compounds with the same and different starting alcohols and therefore different substitution pattern were prepared: 89, 96, 133, 139, 145, 146, 147, 148, 150, 151, 153, 154, 159, 287, 288, 304, 305, 562, 563, 569, 570, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 586, 587, 588, 589, 590, 591, 592, 594, 600, 601, 603, 604, 605, 606, 607, 608, 609, 613, 617, 620, 621, 622, 623, 624, 625, 644 and 649.

In some cases a protecting group had to be removed to obtain the described final compound, e.g. for 595, 598, 602 and 614 (procedure h.).




e. Compound **10** (500 mg, 1.13 mmol) was dissolved in MeOH containing ammonia (10 mL, 5.9 M) and the mixture was stirred at 100°C in a sealed pressure tube for 18 h. After keeping the mixture at RT for 2 h, the crystals formed in the reaction mixture were filtered off, washed with diethyl ether and dried in vacuo. 305 mg (0.84 mmol, 76%) of **12** as a colorless solid were obtained. The compound was used without further purification.

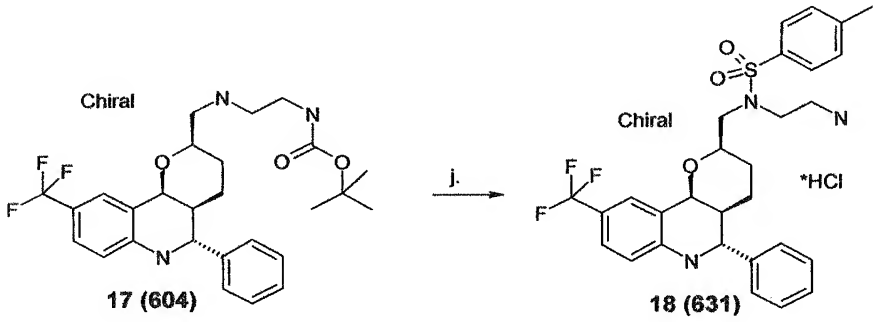
f. The amine **12** (100 mg, 0.28 mmol) and 1,1'-carbonyldiimidazole (49.2 mg, 0.30 mmol) were dissolved in dichloromethane (2 mL) and stirred for 2 h at RT. To this mixture N,N-dimethylethylenediamine (36.5 mg, 0.41 mmol) were added at RT and stirring was continued for additional 18 h at RT. The solvent was evaporated in vacuo, the residue was redissolved in ethyl acetate, and washed twice with water and once with brine. The organic layer was dried with sodium sulfate, filtered and evaporated to dryness. The residue was purified by chromatography (ethyl acetate/methanol, 1:1) to result in **13** (94 mg, 0.20 mmol, 72 %7) as a colorless solid.
According to this procedure the following compounds were prepared: 637, 638, 639 starting from 604, 569 and 603 and deprotection (see procedure h.).

g. The amine **12** (100 mg, 0.28 mmol), 4-methyl morpholine (0.03 mL, 0.28 mmol) and 4-(tert-butoxycarbonylamino)-butyric acid (51 mg, 0.28 mmol) were dissolved in DMF (2 mL). To this solution hydroxybenzotriazole (37.3 mg, 0.28 mmol) and N-(3-diaminopropyl)-N'-ethylcarbodiimid hydrochloride (52.9 mg, 0.28 mmol) were added at RT and stirring was continued for additional 18 h at RT. Water (20 mL) was added and the mixture was extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulfate and the

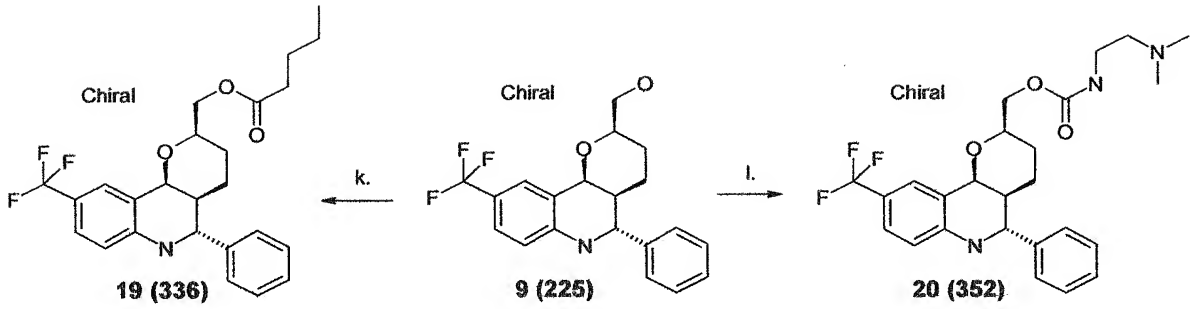
solvent was evaporated in vacuo. The residue was purified by chromatography (ethyl acetate/cyclohexane, gradient) to result in **14** (130 mg, 0.24 mmol, 86%) as a colorless solid. According to this procedure the following compounds were prepared: 227, 244 and 627 starting from 604, 569 and 603, as well as other intermediates that were deprotected directly and therefore described after treatment with procedure h.

h. Compound **14** was dissolved in 5 N HCl in dioxan (2 mL) and stirred for 45 min at RT. The solvent was evaporated in vacuo and the residue was lyophylized to result in colorless **15** (115 mg, 0.28 mmol, 100 %) as a mono hydrochloride salt.
According to this procedure the following compounds were prepared: 243, 272, 629, 630, 634, 635, 636 and 640.

i. Compound **10** (100 mg, 0.23 mmol) was dissolved in 4-hydroxy-1-methylpiperidine (1 mL) and stirred at 100°C in a sealed pressure tube for 18 h. The reaction mixture was poured onto water, the precipitate formed was filtered off, washed with diethyl ether and dried in vacuo. The residue was dissolved in 0.1 M HCl in isopropanol (0.1 mL), the solvent was evaporated in vacuo and the residue crystallized from diethyl ether. 72 mg (0.14 mmol, 64%) of **16** (hydrochloride) as a colorless solid were obtained.
According to this procedure the following compounds were prepared: 349 and 593.

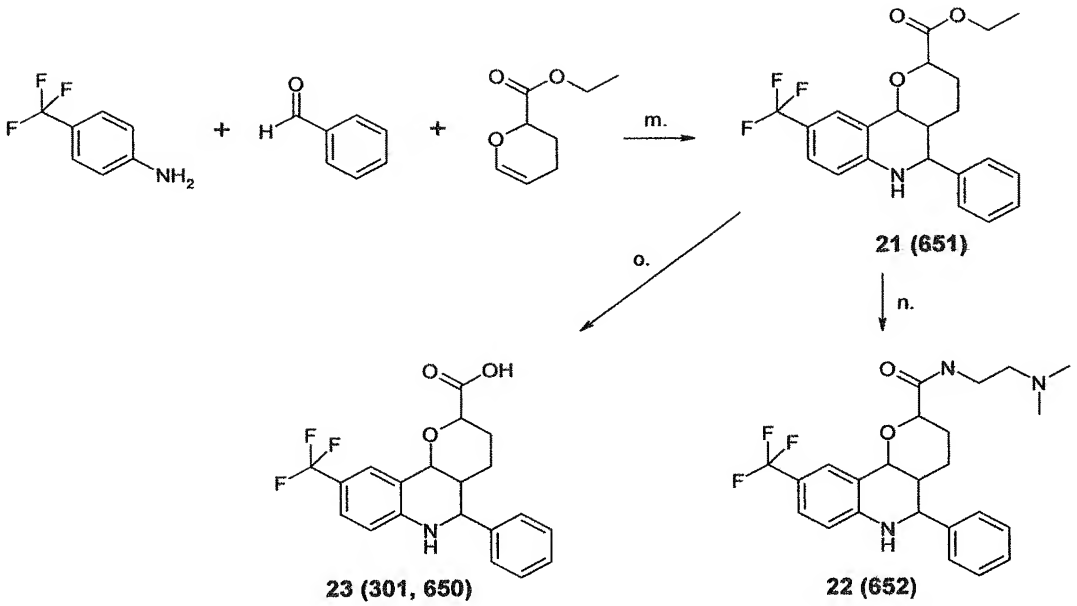



j. The amine **17** (100 mg, 0.20 mmol) and triethyl amine (0.03 mL mg, 0.22 mmol) were dissolved in dichloromethane (2 mL). To this mixture toluene-4-sulfonyl chloride (41.6 mg, 0.22 mmol) dissolved in dichloromethane (1 mL) was added dropwise at RT and stirring was continued for additional 18 h at RT. The solvent was evaporated in vacuo, the residue was redissolved in ethyl acetate, and washed twice with water and once with brine. The organic layer was dried with sodium sulfate, filtered and evaporated to dryness. The residue was purified by chromatography (ethyl acetate/cyclohexane, gradient) and treated according procedure h. 89 mg (0.15 mmol, 68%) of a colorless compound **18** (hydrochloride) were obtained.
According to this procedure the following compounds were prepared: 632 and 633 starting from 569 and 603.




k. The alcohol **9** (100 mg, 0.28 mmol) was suspended in dry tetrahydrofuran (THF, 2 mL), pyridine (87.6 mg, 1.10 mmol) was added at RT, followed by dropwise addition of a solution of valeroyl chloride (36.2 mg, 0.30 mmol) in THF (1 mL) at RT. The solution was stirred for additional 2 h at the same temperature and the solvent was evaporated in vacuo. The residue was redissolved in ethyl acetate (10 mL) and extracted with water twice. The organic phase was dried with sodium sulfate, filtered and evaporated to dryness. The residue was purified by chromatography (ethyl acetate/cyclohexane, gradient) to result in 91.4 mg (0.20 mmol, 94%) of a colorless solid identified as **19**.
According to this procedure compounds 309, 330, 331, 334, 336, 337, 338, 339, 348, 353, 359, 360, 361, 362, 368, 628 and 643 were synthesized.

l. The alcohol **9** (2.00 g, 5.50 mmol) and 1,1'-carbonyldiimidazole (0.98 g, 6.05 mmol) were dissolved in dichloromethane (50 mL) and stirred for 2 h at RT. To this mixture N,N-dimethylethylenediamine (0.58 g, 6.60 mmol) was added at RT and stirring was continued for additional 18 h at RT. Dichloromethane (50 mL) was added and the mixture was washed twice with water and once with brine. The organic layer was dried with sodium sulfate, filtered and evaporated to dryness. The residue was purified by chromatography (ethyl acetate/methanol, 1:1) to result in **20** (2.07 g, 4.35 mmol, 79 %) as a colorless solid.
According to this procedure the following compounds were prepared: 356, 565, 566, 610, 611, 612, 618 (615 after deprotection of 618 according procedure h), 642 and 643.




m. A solution of the mono trifluoroacetic acid salt of 4-aminobenzotrifluoride in acetonitrile - previously prepared by dissolving 4-aminobenzotrifluoride (1.42 g, 8.92 mmol) in acetonitrile (7 mL) and adding slowly trifluoroacetic acid (0.69 mL; 8.92 mmol) at 0°C – was added to a solution of benzaldehyde (0.95 g, 8.92 mmol) and 3,4-dihydro-2H-pyran-2-carboxylic acid ethyl ester (1.39 g, 8.92 mmol) in acetonitrile (9 mL) at RT. The solution was stirred at RT for 18 h. The solvent was removed in vacuo. The residue was directly purified by chromatography (ethyl acetate/cyclohexane, gradient). 1.20 g (2.96 mmol, 33 %) of a colorless solid identified as compound **21** were obtained.

n. Compound **21** (100 mg, 0.25 mmol) was dissolved in N,N-diethylethylenediamine (1 mL) and stirred at 100°C in a sealed pressure tube for 18 h. To the reaction mixture ethyl acetate was added and washed with water 3 times and with brine once. The organic layer was dried with sodium sulfate, filtered and evaporated to dryness. The residue was purified by chromatography (ethyl acetate/methanol, 1:1) to result in **22** (64.1 mg, 0.14 mmol, 58 %) as a colorless solid.

o. Compound **21** (200 mg, 0.49 mmol) was dissolved in THF (10 mL) and water was added (5 mL). LiOH (47.3 mg, 1.97 mmol) were added and the mixture was stirred at reflux for 2 h. Diluted HCl solution (2N) was added to adjust the ph at 1-2. To this mixture ethyl acetate was added, the organic layer separated and washed with water and with brine. The organic layer was dried with sodium sulfate, filtered and evaporated to dryness to result in **23** (185 mg, 0.14 mmol, 99 %) as a colorless solid.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

February 04, 2010.....

Date

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Kai Schiemann